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(71) Applicant
Merck & Co Inc

(Incorporated in the USA – New Jersey)

P O Box 2000, 126 East Lincoln Avenue, Rahway, New Jersey 07065-0900, United States of America

(72) Inventors
Prasun K Chakravarty
Richard W Ransom

(74) Agent and/or Address for Service
W G Cole
Merck & Co Inc, European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, United Kingdom

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A5B BHA B180 B33Y B332 B42Y B421 B422 B424 B425 B48Y B480 B481 B482 B484 B49Y B490 B493 B50Y B503 B504 B505 B51Y B510 B54Y B542 B56Y B565 B58Y B586 B59Y B596 B61Y B616 B64Y B640 B646 B65X B65Y B650 B652 B654 B655 B66Y B661 B823 B828 B829
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(56) Documents cited
EP 0409332 A2 US 5155126 A US 5015651 A

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UK CL (Edition L) A5B BHA BJA
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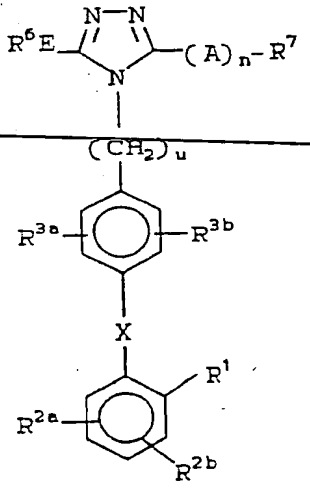
(54) Substituted triazoles as neurotensin antagonists

(57) Substituted triazoles of the formula (I) as disclosed in EP-0409332-A2, are as neurotensin antagonists useful in the treatment of certain CNS and GI disorders.



(I)

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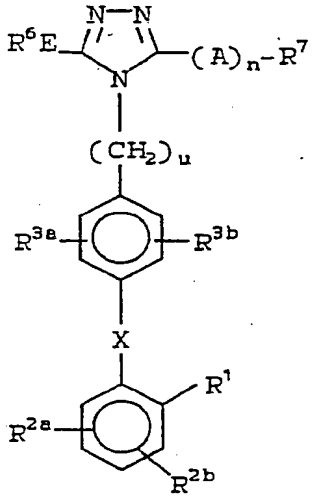
TITLE OF THE INVENTION

SUBSTITUTED TRIAZOLES AS NEUROTENSIN ANTAGONISTS

INTRODUCTION OF THE INVENTION

This invention is concerned with a method of treating disease states mediated by neurotensin by the administration to a patient in need of treatment of a therapeutically effective amount of a neurotensin antagonist which is a substituted triazole of structural formula I:



(I)

As neurotensin antagonists these compounds find utility in the treatment of CNS dysfunctions such as psychoses, depression, cognitive dysfunction, such as Alzheimer's disease, anxiety, tardive dyskinesia, drug dependency, panic attack and mania. The neurotensin antagonist property also imparts to the compounds utility in GI disorders such as gastroesophageal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis. The known ability of neurotensin to release mast cell histamine indicates that antagonists will be useful in the treatment of allergic and inflammatory conditions.

BACKGROUND OF THE INVENTION

Neurotensin (NT) is a tridecapeptide hormone (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH), originally isolated from the bovine hypothalamus [Carraway, R. and Leeman, S. E., J. Biol. Chem.,248, 6854 (1973)], has subsequently been shown to be distributed in the brain [Uhl, G. R., et al., Proc. Natl. Acad. Sci. USA, 74, 4059-4063 (1977), gastrointestinal tract [1). Kitabgi, P., Carraway, R. and Leeman, S. E., J. Biol. Chem., 251, 7053 (1976); 2). Carraway, R., Kitabgi, P., and Leeman, S. E., J. Biol. Chem., 253, 7996 (1978); 3).Helmstadler, V., Taugner, C., Feurle, G. E. and Frossman, W. G., Histochemistry, 53, 35-41 (1977)] and pancreas [Feurle, G. E. and Niestroj, S., Pancreas, 6, 202-207 (1991) and references cited therein] of various animals including human [Mai, J. K., et al., Neuroscience, 22, 499-524 (1987)]. Although the physiological role of neurotensin has

not yet been clearly understood, this endogenous peptide participates in a wide spectrum of central [1). Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-375 (1982); 2). Stowe, Z. N.and Nemeroff, C. B., Life Sci., 49, 987-1002, (1991); 3) Kitabgi, P., Neurochem. Int., 14, 111-119 (1989); 4). Levant and Nemeroff, C. B., Current topics in Neuroendocrinology, 8, 231-262 (1988)] and peripheral [Leeman, S. E., Aronin, N. and Ferris, C., Hormone Res., 38, 93-132 (1982)] biological functions.

Neurotensin is also known to release mast cell histamine, indicating that antagonists will be useful in the treatment of allergic and inflammatory conditions, as well. [See, Rossei, S.S. and Miller, R.J., Life Sci., 31, 509-516 (1982) and Kurose, M. and Saeki, K., Eur. J. Pharmacol., 76, 129-136 (1981).]

Neurotensin, like most other peptides, is unable to cross the blood-brain barrier (BBB). However, certain peripheral effects of neurotensin have been observed after central administration of the peptide [Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-391 (1982). The direct application of neurotensin into the brain causes hypothermia, potentiation of barbiturate induced sedation, catalepsy, antinociception, blockade of psychostimulant-induced locomotor activity and reduced food consumption. In the central nervous system (CNS), neurotensin behaves as a neurotransmitter or neuromodulator [1) Uhl, G. R. and Snyder, S. H., Eur. J. Pharmacol., 41, 89-91 (1977); 2) Uhl, G. R., Annal. NY Acad. Sciences, 400,

132-149 (1982)], and has been shown to have close anatomical and biochemical associations with the dopaminergic (DA) system [Nemeroff, C. B., et al. Annal. NY Acad. Sciences, **400**, 330-344 (1982)]. Neurotensin increases the synthesis and the turnover of DA in rat brain. Acute and chronic treatment with clinically efficacious antipsychotic drugs (e.g., haloperidol, chloropromazine) have consistently demonstrated an increase in neurotensin concentrations in the nucleus accumbens and striatum while phenothiazines that are not antipsychotics did not produce this increase. Behaviorally, neurotensin, after central administration, mimics the effects of systemically administered neuroleptics. However, unlike classical neuroleptics (which primarily acts on D_2 receptors), neurotensin fails to bind to dopamine receptors or inhibit cAMP accumulation following DA receptor activation. Neurotensin does not block the stereotypy induced by DA agonists. The post-mortem studies of patients with schizophrenia showed an increase in the level of neurotensin in the Brodman's area 32 of human brain [Nemeroff, C. B., et. al., Science., **221**, 972-975 (1983) and references cited therein], which suggest possible roles of neurotensin in the pathophysiology of this disease. Neurotensin receptors have also been implicated in Parkinson's disease and progressive supranuclear palsy [Chinaglia, G. et al., Neuroscience, **39**, 351-360 (1990)].

Of the total body neurotensin in many mammalian species, more than 80% is present in the gastrointestinal tract, especially in the distal small intestine in the endocrine like N-cells. In the

gut, neurotensin stimulates pancreatic secretion [Sakamoto, T.,et al, Surgery, **96**, 146-53 (1984)], inhibits gastric acid secretion and gastric emptying [Blackburn, A. M., Lancet, **1**, 987-989 (1980)]. Neurotensin also stimulates the growth of small intestinal mucosa in an isolated defunctional loop of jejunum, which suggests a direct systemic effect of neurotensin in the gut. In addition, neurotensin can stimulate pancreatic exocrine secretion in mammals [Iwatsuki, K., et al., Clin. Expt. Pharmacol. Physiol., **18**, 475-481 (1991) and references cited therein].

From the structural work, it is evident that the biological activity of neurotensin resides within the carboxy terminal five or six amino acid residues. The C-terminal hexapeptide NT^{8-13} has displayed full biological activity of the tridecapeptide. In contrast, all amino terminal partial sequences are essentially inactive [Leeman, S. E. and Carraway, R. E., Annal. NY Acad. Sciences, **400**, 1-16 (1982)]. The C-terminal COOH group and two Arg residues are essential for the biological activity of NT^{8-13} as well as neurotensin. L-amino acids are required at positions-9,10,11 and 13, and only Arg^8 can be replaced by D-Arg without loss of any activity. At the position-11, an aromatic amino acid is essential. Similarly, alkyl side-chains of Ile^{12} and Leu^{13} are also necessary for full biological activity [Kitabgi, P., Annal. NY Acad. Sciences, **400**, 37-53 (1982)]. Most of the analogues of neurotensin examined generally behaved as agonists. However, two analogues $D\text{-}Trp^{11}$-NT and $Tyr(Me)^{11}$-NT have displayed partial antagonist activity [Rioux, F. R.,et al., Eur. J. Pharmacol., **66**, 373-379 (1980)].

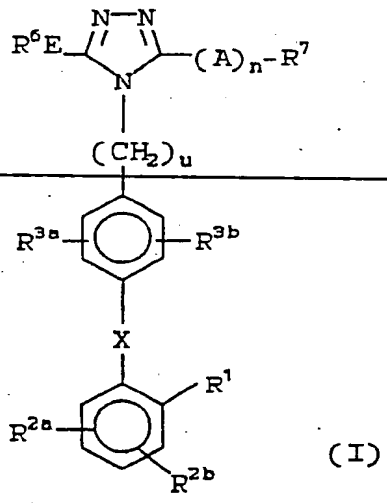
The compounds useful in the novel method of treatment of this invention are known in the art having been published in European Patent Application EP 409,332 (Merck & Co., Inc.) where they are alleged to be angiotensin-II (A-II) receptor antagonists useful in the treatment of hypertension, ocular hypertension.

Although there are reports of peptidic neurotensin antagonists, they are unstable and not orally active and none are clinically available. There are no reports of non-peptidic neurotensin antagonists.

Now with this invention, there are provided non-peptidic neurotensin antagonists.

DETAILED DESCRIPTION OF THE INVENTION

This compounds useful in the novel method of treatment of this invention have structural formula I:



(I)

pharmaceutically acceptable salt thereof

wherein:

R^1 is

(a) $-NHSO_2R^{23}$,
(b) $-NHSO_2NHCOR^{23}$,
(c) $-NHCONHSO_2R^{23}$,
(d) $-SO_2NHR^{23}$,
(e) $-SO_2-NHCOR^{23}$,
(f) $-SO_2NHCONR^9R^{23}$
(g) $-SO_2NHCOOR^{23}$
(h) $-SO_2NHOR^{23}$,
(i) $-CH_2SO_2NHCOR^{23}$,
(j) $-CH_2SO_2NHCOR^{23}$,
(k) $-CO_2H$, or
(l) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are each independently:

(a) hydrogen,
(b) Cl, Br, I, F,
(c) CF_3,
(d) C_1-C_4-alkyl,
(e) C_1-C_4-alkoxy; or

R^{3a} is

(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy,
(e) C_1-C_6-alkoxy-C_1-C_4-alkyl;

R^{3b} is

(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,

(d) C_3-C_6-cycloalkyl,
(e) C_1-C_6-alkoxy, or
(f) CF_3;

R^4 is H, C_1-C_6-alkyl, benzyl or phenyl;

R^5 is H, $-CH(R^4)-O-C(=O)-R^4$;

E is a single bond, $-NR^{13}(CH_2)_s-$, $-S(O)_x(CH_2)_s-$ where x is 0 to 2 and s is 0 to 5, $-CH(OH)-$, $-O(CH_2)_s-$, $-CO-$;

R^6 is

(a) aryl wherein aryl is defined as phenyl or naphthyl which can be unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, C_3-C_7-cycloalkyl, and C_2-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which can be unsubstituted substituted with a substituent selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, $-OH$, $-O-C_1-C_4$-alkyl, $-NH_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, $-S-C_1-C_4$-alkyl; or

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered heterocycle which contains one or two heteroatoms selected from the group

consisting of N, O and S, and wherein the substituents are members selected from the group consisting of -OH, -SH, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, Cl, Br, I, F, or NO_2;

(d) mono-, di-, tri- or perfluoro-C_1-C_5-alkyl;

(e) C_3-C_7-cycloalkyl, unsubstituted or substituted with one or more substituents selected from the group consisting of C_1-C_4-alkyl, -O-C_1-C_4-alkyl, -S-C_1-C_4-alkyl, -OH, perfluoro-C_1-C_4-alkyl, or Cl, Br, F, I;

(f) C_3-C_7-cycloalkyl-C_1-C_3-alkyl wherein the cycloalkyl is substituted as in (e) above,

A is $S(O)_p$, -O- NHC(=O)-, $-C(=O)NR^{13}-$, or $-NR^{13}-$, wherein p is 0 to 2;

R^7 is

(a) C_1-C_{10}-alkyl,

(b) substituted C_1-C_{10} alkyl in which one or more substituent(s) is selected from

(1) Cl, Br, I, F,

(2) hydroxy,

(3) C_1-C_{10}-alkoxy,

(4) C_1-C_5-alkoxycarbonyl,

(5) C_1-C_4-alkylcarbonyloxy,

(6) C_3-C_8-cycloalkyl,

(7) phenyl,

(8) substituted phenyl in which the substituents are V and W,

(9) C_1-C_{10}-alkyl-$S(O)_p$,

(10) C_3-C_8-cycloalkyl-$S(O)_p$,

(11) phenyl-$S(O)_p$,

(12) substituted phenyl-$S(O)_p$ in which the substituents are V and W,
(13) oxo,
(14) carboxy,
(15) NR^9R^{10},
(16) C_1-C_5-alkylaminocarbonyl,
(17) di(C_1-C_5-alkyl)aminocarbonyl,
(18) cyano;

(c) perfluoro-C_1-C_4-alkyl,
(d) C_2-C_{10}-alkenyl,
(e) C_2-C_{10}-alkynyl,
(f) C_3-C_8-cycloalkyl,
(g) substituted C_3-C_8-cycloalkyl in which one or more substituent(s) is selected from the group:
(1) I, Br, Cl, F,
(2) hydroxy,
(3) C_1-C_{10}-alkoxy,
(4) C_1-C_5-alkoxycarbonyl,
(5) C_1-C_4-alkylcarbonyloxy,
(6) C_3-C_8-cycloalkyl,
(7) phenyl,
(8) substituted phenyl in which the substituents are V and W,
(9) C_1-C_{10}-alkyl-$S(O)_p$ in which p is 0 to 2,
(10) C_3-C_8-cycloalkyl-$S(O)_p$,
(11) phenyl-$S(O)_p$,
(12) substituted phenyl-$S(O)_p$ in which the substituents are V and W,
(13) oxo,
(14) carboxy,
(15) NR^9R^{10},
(16) C_1-C_5-alkylaminocarbonyl;
(17) di(C_1-C_5-alkyl)aminocarbonyl;

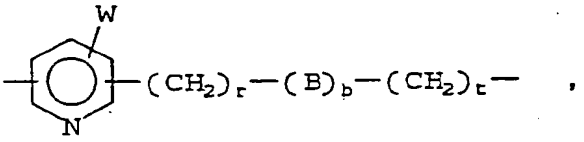
(18) cyano,
(19) C_1-C_4-alkylcarbonyl,
(20) (C_1-C_5)-alkyl,

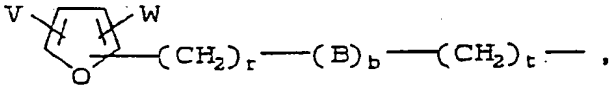
(h) phenyl,

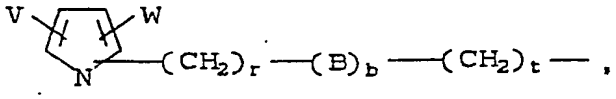
(i) substituted phenyl in which the substituents are V and W,

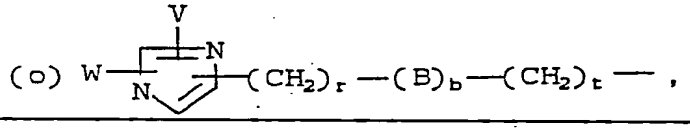
(j) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-

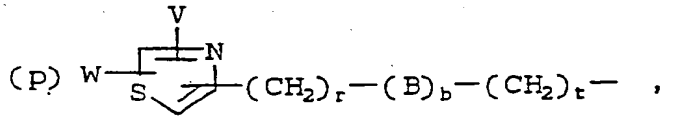
(k) substituted phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which the phenyl group is substituted with V and W;

(l) 

(m) 

(n) 

(o) 

(p) 

with the proviso that when E is a single bond and n is 0, then R^7 is:

(a) substituted C_1-C_{10}-alkyl in which one or more substituent(s) is selected from:
(1) C_3-C_8-cycloalkyl,
(2) phenyl,

(3) substituted phenyl as defined above in which the substituents are V and W,

(4) C_3-C_8-cycloalkyl-$S(O)_p$ where p is 0 to 2,

(5) phenyl-$S(O)_p$ where p is 0 to 2,

(6) substituted phenyl-$S(O)_p$ where p is 0 to 2 and the substituents are V and W;

(b) CF_3;

(c) C_3-C_8-cycloalkyl;

(d) substituted C_3-C_8-cycloalkyl in which the substituent is selected from:

(1) C_1-C_5-alkyl,

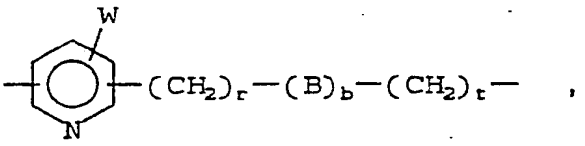
(2) C_1-C_5-alkoxy;

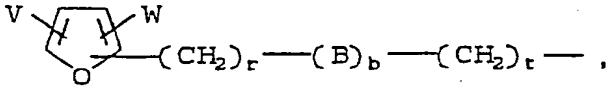
(e) phenyl,

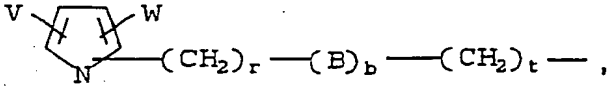
(f) substituted phenyl in which the substituents are V and W;

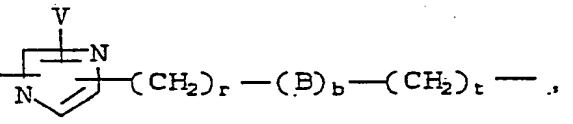
(g) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which b is 0 when B is -C(O)-;

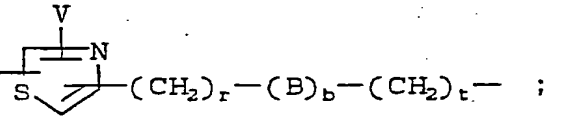
(h) substituted phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which b is 0 when B is -C(O)- and the phenyl group is substituted with V and W;

(i)  ,

(j)  ,

(k)  ,

(l)  ,

(m)  ;

n is 0 or 1;

B is -C(O)-, -S-, -O-, $-NR^4$, $-NR^4C(O)-$, or $-C(O)NR^4$;

b is 0 or 1;

r and t are 0 to 2;

u is 1 or 2;

p is 0 to 2;

V and W are each independently selected from:

(a) H,
(b) C_1-C_5-alkoxy,
(c) C_1-C_5-alkyl,
(d) hydroxy,
(e) C_1-C_5-alkyl-$S(O)_p$,
(f) -CN,
(g) $-NO_2$,
(h) $-NR^9R^{10}$,
(i) C_1-C_4-alkyl-$CONR^9R^{10}$,
(j) $-CO_2R^9$,
(k) C_1-C_5-alkyl-carbonyl,
(l) trifluoromethyl,
(m) Cl, Br, I, F,
(n) hydroxy-C_1-C_4-alkyl-,
(o) C_1-C_4-alkyl-CO_2R^9,
(p) -1H-tetrazol-5-yl,
(q) $-NH-SO_2CF_3$;
(r) aryl,
(s) $-OCONR^9R^{10}$,
(t) $-NR^4CO_2R^9$,
(u) $-NR^4CONR^9R^{10}$,
(v) $-NR^4CON(CH_2CH_2)_2Q$ where Q is O, $S(O)_p$ or NR^9,
(w) $-OCON(CH_2CH_2)_2Q$, or
(x) $-CONR^9R^{10}$;

R^9 is H, C_1-C_5-alkyl, phenyl or benzyl;

R^{10} is H, C_1-C_4-alkyl;

or R^9 and R^{10} together may be $-(CH_2)_m-$ where m is 3-6;

R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, or $-CH_2-C_6H_4R^{20}$;

R^{12} is $-CN$, $-NO_2$ or $-CO_2R^4$;

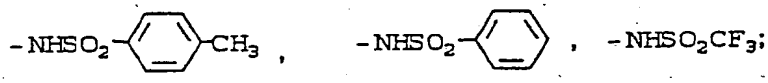
R^{13} is H, C_1-C_4-acyl, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{15} is H, C_1-C_6-alkyl, hydroxy;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, $-OH$ or $-OCH_3$;

R^{21} is C_1-C_5-alkyl or CF_3;

R^{22} is

(a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, or F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, $-COOR^4$, C_3-C_7-cycloalkyl, and C_3-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, $-OH$, $-O-C_1-C_4$-alkyl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, and $-S-C_1-C_4$-alkyl;

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring comprising one or two heteroatoms selected from the group consisting of N, O, and S, and wherein the substituents are members selected from the group consisting of: $-OH$, $-SH$, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, $-COOR^4$, Cl, Br, I, F, and NO_2; or

(d) C_3-C_7-cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of:

C_1-C_4-alkyl, -O-C_1-C_4-alkyl, -S-C_1-C_4-alkyl, -OH, -$COOR^4$, C_1-C_4-perfluoroalkyl, Cl, Br, F, and I, or

(e) (C_1-C_4)-perfluoroalkyl;

R^{23} is

(a) aryl,

(b) heteroaryl,

(c) C_3-C_7-cycloalkyl,

(d) C_1-C_4-alkyl, unsubstituted or substituted with a substituent selected from the group consisting of aryl, heteroaryl as defined above, -OH, -SH, C_1-C_4-alkyl, -O(C_1-C_4-alkyl), -S(C_1-C_4-alkyl), $-CF_3$, Cl, Br, F, I, $-NO_2$, $-CO_2H$, $-CO_2$-C_1-C_4-alkyl, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, -N$(CH_2CH_2)_2$L where L is a single bond, CH_2, O, $S(O)_p$ or NR^9, $-PO_3H$, -PO(OH)(O-C_1-C_4-alkyl);

X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $-\underset{\displaystyle R^{13}}{N}-$,

(f) $-CO\underset{\displaystyle R^{15}}{N}-$,

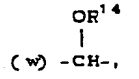
(g) $-\underset{\displaystyle R^{15}}{N}CO-$,

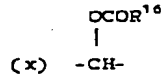
(h) $-OCH_2-$,

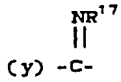
(i) $-CH_2O-$

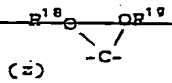
(j) $-SCH_2-$,

(k) $-CH_2S-$,
(l) $-NHC(R^9)(R^{10})-$,
(m) $-NR^9SO_2-$,
(n) $-SO_2NR^9-$,
(o) $-C(R^9)(R^{10})NH-$,
(p) $-CH=CH-$,
(q) $-CF=CF-$,
(r) $-CH=CF-$,
(s) $-CF=CH-$,
(t) $-CH_2CH_2-$,
(u) $-CF_2CF_2-$,
(v) 1,1 and 1,2-disubstituted cyclopropyl,


(w)


(x)


(y) , or


(z) ;

Z is O, NR^{13} or S.

The terms "alkyl", "alkenyl", "alkynyl: and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

One embodiment of the compounds of Formula (I) are those compounds wherein:

R^1 is

(a) $-SO_2NHCOR^{23}$,
(b) $-SO_2NHCONR^9R^{23}$,
(c) $-SO_2NHCOOR^{23}$,
(d) $-SO_2NHOR^{23}$,
(e) $-CH_2SO_2NHCOR^{23}$, or
(f) -1H-tetrazol-5-yl;

R^{2a} is H;

R^{2b} is H, F, Cl, CF_3 or C_1-C_4-alkyl;

R^{3a} is H;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1-C_4-alkyl)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_6-alkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, OH, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ and phenyl;

(b) C_2-C_6-alkenyl or C_2-C_6-alkynyl;

(c) aryl either unsubstituted or substituted with a substituent selected from the group consisting of halo (Cl, F, Br, I), $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-S-CH_3$, $-S-C_2H_5$, $-SO_2NH_2$ and $-O-CH_3$;

(d) a heteroaryl selected from the group consisting of 2-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, imidazoyl, thiazolyl, thienyl, or furyl;

(e) perfluoro-C_1-C_4-alkyl selected from CF_3, CF_3CF_2, $CF_3CF_2CF_2$, $CF_3CF_2CF_2CF_2$;

(f) C_3-C_7-cycloalkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, OH, $-O-CH_3$, $-O-C_2H_5$, $-S-CH_3$, $-S-C_2H_5$, CH_3, CH_2CH_3, CF_2CF_3, $(CF_2)_2CF_3$ and phenyl;

R^7 is:

(a) C_1-C_{10}-alkyl,

(b) substituted C_1-C_{10}-alkyl in which one or two substituents are selected from:

(1) hydroxy,

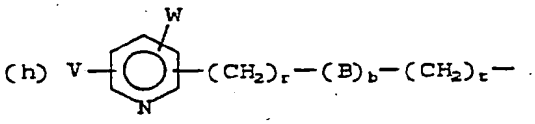
(2) C_1-C_5-alkoxy,

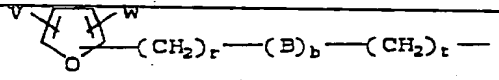
(3) C_1-C_5-alkoxycarbonyl,

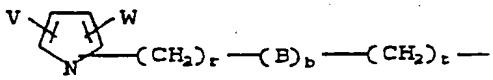
(4) C_1-C_4-alkylcarbonyloxy,

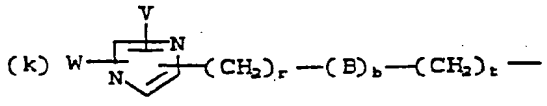
(5) C_3-C_8-cycloalkyl,
(6) phenyl,
(7) substituted phenyl in which the substituents are V and W,
(8) C_1-C_5-alkyl-$S(O)_p$,
(9) phenyl-$S(O)_p$,
(10) substituted phenyl-$S(O)_p$ in which the substituents are V and W,
(11) oxo,
(12) carboxy,
(13) C_1-C_5-alkylaminocarbonyl, or
(14) di(C_1-C_5-alkyl)aminocarbonyl;

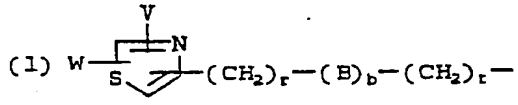
(c) CF_3,
(d) phenyl,
(e) substituted phenyl in which the substituents are V and W,
(f) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,
(g) substituted phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,

(h) 

(i) 

(j) 

(k) 

(l) 

A is -S-, -S(O)- or -O-;

V and W are independently selected from:

(a) hydrogen,
(b) C_1-C_5-alkoxy,
(c) C_1-C_5-alkyl,
(d) hydroxy,
(e) NR^9R^{10},
(f) CO_2R^9,
(g) trifluoromethyl,
(h) Cl, Br, I, F,
(i) hydroxy-C_1-C_4-alkyl,
(j) -1H-tetrazol-5-yl,
(k) $-NH-SO_2CF_3$,
(l) -CN,
(m) $-NO_2$,
(n) C_1-C_5-alkyl-$S(O)_p$,
(o) C_1-C_4-alkyl-$CONR^9R^{10}$,
(p) C_1-C_5-alkylcarbonyl, or
(q) $-CONR^9R^{10}$;

u is 1;

X is:

(a) ~~carbon-carbon single bond,~~
(b) -C(O)-, or
(c) $-NR^{15}C(O)-$.

In one class of this embodiment are those compounds of formula (I) wherein:

E is a single bond or -S-;

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H;

R^6 is C_1-C_6-alkyl.

Illustrating this class are those compounds of formula (I) wherein:

R^7 is:

(a) C_1-C_{10}-alkyl,

(b) substituted C_1-C_{10}-alkyl in which one or two substituents are selected from:

(1) hydroxy,

(2) C_1-C_5-alkoxy,

(3) C_1-C_5-alkoxycarbonyl,

(4) phenyl,

(5) carboxy,

(6) C_1-C_5-alkylaminocarbonyl;

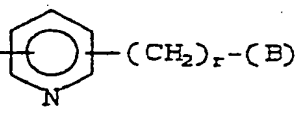
(c) CF_3;

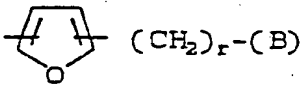
(d) phenyl;

(e) phenyl substituted with V and W;

(f) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-;

(g) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which the phenyl is substituted with V and W;

(h)  or

(i)  ;

V and W are selected from:

(a) hydrogen,
(b) C_1-C_5-alkyl,
(c) C_1-C_5-alkoxy,
(d) CO_2R^9,
(e) halogen,
(f) hydroxy-C_1-C_4-alkyl,
(g) -1H-tetrazol-5-yl,
(h) $-NH-SO_2CF_3$;
(i) -CN,
(j) $-NO_2$; and

X is $-NR^{15}C(O)-$ or a carbon-carbon single bond.

The compounds of Formula (I) can be synthesized using the reactions and techniques described in published European Patent Application EP 409,332 (Merck & Co. Inc.) and EP 323,841 (E.I. DuPont De Nemours & Co.). The above mentioned application discloses the compounds of this invention where they are alleged to be angiotensin II receptor antagonists useful in the treatment of hypertension and ocular hypertension.

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and in the reactants being employed should be consistent with the chemical transformations being conducted. Depending upon the reactions and techniques employed, optimal yields may require changing the order of synthetic steps or use of protecting groups followed by deprotection.

The compounds useful in the novel method treatment of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkai metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic.

The salts can be formed by conventional means, such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Neurotensin is a peptide hormone and the assays described below have been developed to identify neurotensin antagonists and to determine their efficacy in vitro. The following three assays have been employed for that purpose.

RAT FOREBRAIN RECEPTOR ASSAY

Male rats are sacrificed by decapitation following ether anesthetization. Forebrains are homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 µM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 µg/ml bacitracin, 5 µM levocabastine HCl, 1mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenyl methyl sulfonyl fluoride. Assay tubes (13 X 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin 3) 20 µl test compounds 4) 750 µl tissue suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvestor with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 X 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 X 75 mM polypropylene tubes for counting on as Packard Multi-Prias gamma counter.

HUMAN HT-29 CELL MEMBRANE ASSAY

HT-29 cells were routinely grown in 225 cm^2 Costar tissue culture flasks at 37°C in a humidified atmosphere of 5% CO_2/95% air in Dulbecco's modified Eagle's medium with high glucose containing 50 U/ml penicillin, 50 µg/ml streptomycin, 5% fetal bovine serum and 5% newborn calf serum. Cells were subcultured with 0.25% trypsin at a ratio of 1:6 with confluence being reached at 48 to 72 hrs. Cells from confluent flasks (approx. 1 x 10^8 cells/flask) were harvested by scraping. The cells were pelleted by centrifugation (1000 x g, 5 min), resuspended in 50 mM Tris HCl, pH 7.4, and homogenized with a polytron (setting 7 for 10 sec.). Cell membranes were washed twice by centrifugation (50,000 x g, 15 min) and rehomogenization. The resulting pellet was either frozen at -70°C for future use or run directly in the assay by resuspending at a concentration of 0.5 x 10^6 cells per 0.750 ml of assay buffer (50 mM Tris HCl, pH 7.4, containing 1 mM EDTA, 40 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenylmethylsulfonyl fluoride).

Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin 3) 20 µl test compounds 4) 750 µl cell membrane suspension an 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temperature, the samples are filtered using a Brandel M24 cell harvestor with GF/B filtermats that have been presoaked in 0.2%

polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a Packard Multi-Prias gamma counter. [The above assay is derived from the assay described in Kitabgi, P. et al., Molecular Pharmacology, 18, 11-19 (1980)].

NEUROTENSIN BINDING ASSAY USING HUMAN FRONTAL CORTEX

Post-mortem human brain is obtained through the National Disease Research Interchange (Philadelphia, PA). The donors were without psychiatric or neurological abnormalities. Frontal cortex is dissected free of white matter and homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 mM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenyl methyl sulfonly fluoride. Assay tubes (13 x 100 polypropylene) receive 1) 100 µl buffer or 10 µM neurotensin (for non-specific binding) 2) 100 µl of 60 pM [^{125}I]neurotensin
3) 20 µl test compounds 4) 750 µl tissue suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvestor with GF/B

filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a Packard Multu-Prias gamma counter.

Using the methodology described above, representative compounds of the invention were evaluated and all were found to exhibit an activity of at least $IC_{50}<50\mu M$ thereby demonstrating and confirming the utility of the compounds of the invention as effective neurotensin antagonists.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage

unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occuring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples further illustrate the preparation of the compounds of Formula I and their incorporation into pharmaceutical compositions and, as such, are not to be considered or construed as limiting the invention recited in the appended claims.

3-n-Butyl-5-(4-chlorobenzylthio)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4H-1,2,4-triazole (Example 15)

3-n-Butyl-5-(4-chlorobenzylsulfinyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 16)

3-n-Butyl-5-(4-chlorobenzylsulfonyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 17)

3-n-Butyl-5-(4-nitrobenzylthio)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 18)

3-n-Butyl-5-(4-nitrobenzylsulfinyl)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 19)

3-n-Butyl-5-(cyclohexylmethylthio)-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 20)

3-n-Butyl-5-(4-chlorobenzylthio)-4-[4-[2-(1H-tetrazol-5-yl)benzamido]benzyl]-4H-1,2,4-triazole (Example 21)

3-n-Butyl-5-(4-chlorobenzylsulfinyl)-4-[4-[2-(1H-tetrazol-5-yl)benzamido]benzyl]-4H-1,2,4-triazole (Example 22)

3-n-Butyl-5-methylthio-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 22)

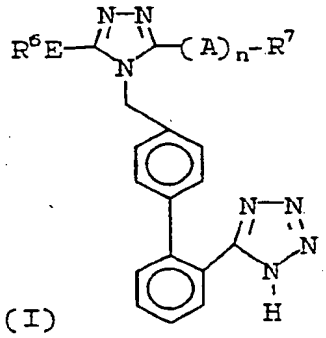
3-n-Butyl-5-methylsulfonyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole Example 24)

3-Benzyloxy-5-n-butyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-1,2,4-triazole (Example 25)

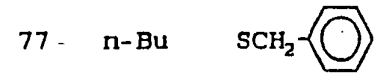
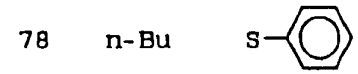
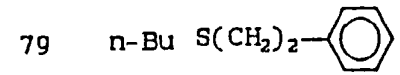
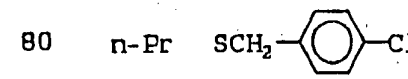
3-(N-Benzyl-N-methylcarbamoyl)-5-n-butyl-4-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4H-1,2,4-triazole (Example 26)

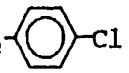
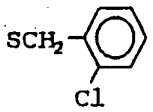
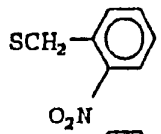
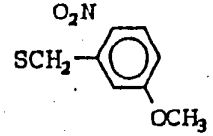
EXAMPLES 77-92

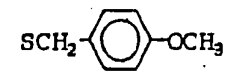
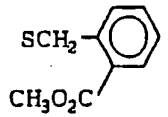
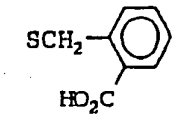
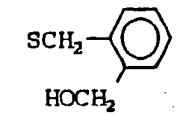
The following compounds of formula (I) were prepared following the procedures of Examples 15-20 and 23-26 and Schemes 1-14, 17 and 18 in EP application 409,332.

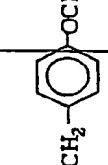
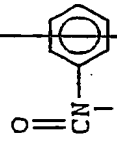


(I)

	R^6E	$R^7-(A)_n-$	mp	formula		Analysis C	H	N
77	n-Bu		107°C dec	$C_{27}H_{27}N_7S \cdot 0.5H_2O$ $\cdot 0.05CH_2Cl_2$	calcd:	65.65	5.72	19.82
					found:	65.64	5.64	19.54
78	n-Bu		84-85°C dec	$C_{26}H_{25}N_7S \cdot 0.75H_2O$ $\cdot 0.15CH_2Cl_2$	calcd:	64.02	5.50	20.03
					found:	64.30	5.50	19.72
79	n-Bu		79-80°C	$C_{28}H_{29}N_7S \cdot 0.75H_2O$	calcd:	66.05	6.04	19.26
					found:	66.32	5.92	19.16
80	n-Pr		90-92°C	$C_{26}H_{24}ClN_7S \cdot 0.2H_2O$ $\cdot 0.8CH_4O$ (methanol)	calcd:	60.58	5.24	18.46
					found:	60.65	5.15	18.10

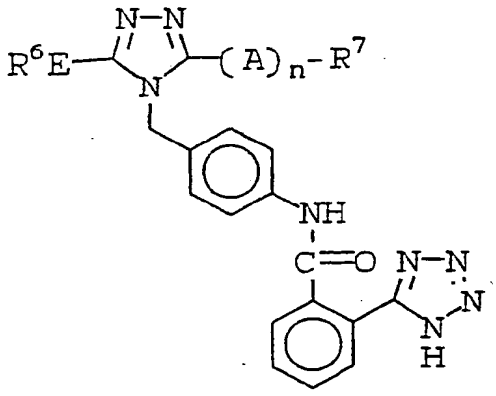
	R^6E	$R^7-(A)_n-$	mp	formula	Analysis	C	H	N
81	n-Pentyl		97-99°C	$C_{28}H_{28}ClN_7S \cdot 0.75H_2O$	calcd:	61.86	5.45	18.04
					found:	61.85	5.41	18.12
82	n-Bu		79-80°C	$C_{27}H_{26}ClN_7S \cdot 0.1CH_2Cl_2$	calcd:	62.06	5.03	18.70
					found:	62.34	5.24	18.58
83	n-Bu		115°C dec	$C_{27}H_{26}N_8O_2S \cdot 0.75H_2O$	calcd:	60.03	5.13	20.75
					found:	59.93	5.13	20.47
84	n-Bu		78-80°C	$C_{28}H_{29}N_7OS$				

	R^6E	$R^7-(A)_n-$	mp	formula	Analysis	C	H	N
85	n-Bu		95-97°C	$C_{28}H_{29}N_7OS$				
86	n-Bu		120-122°C dec	$C_{29}H_{29}N_7O_2S \cdot 1.5H_2O \cdot 0.2CH_2Cl_2$	calcd: found:	59.62 59.77	5.55 5.44	16.67 16.44
87	n-Bu		203-204°C dec	$C_{28}H_{27}N_7O_2S$				
88	n-Bu		93-95°C	$C_{28}H_{29}N_7OS \cdot 0.3H_2O \cdot 0.25CH_2Cl_2$	calcd: found:	63.03 63.29	5.64 5.92	18.22 17.89

	R^6E	$R^7-(A)_n-$	mp	Formula	Analysis	C	H	N
89	n-Bu	$SCH_2CH(CH_3)_2$	90-91°C	$C_{24}H_{29}N_7S \cdot 0.15CH_2Cl_2$	calcd:	63.00	6.42	21.30
					found:	63.07	6.50	21.00
90	n-Bu		125-126°C	$C_{28}H_{29}N_7O_2S$				
91	n-Bu		106-107°C	$C_{21}H_{23}N_7OS$				
92	n-Bu		100°C	$C_{28}H_{28}N_8O \cdot 0.15CH_2Cl_2$	calcd:	66.91	5.65	22.18
					found:	67.27	5.90	21.82

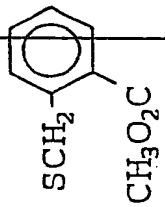
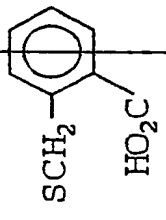
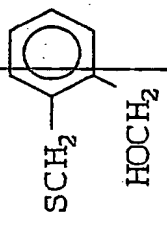
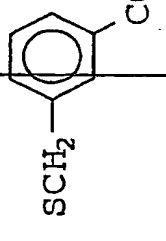
EXAMPLES 93-108

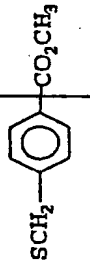
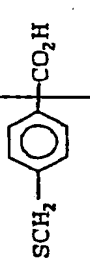
The following compounds of formula (I) were or can be prepared following the procedure of Examples 21 and 22 and Schemes 1-15, 18 and 19.

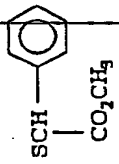


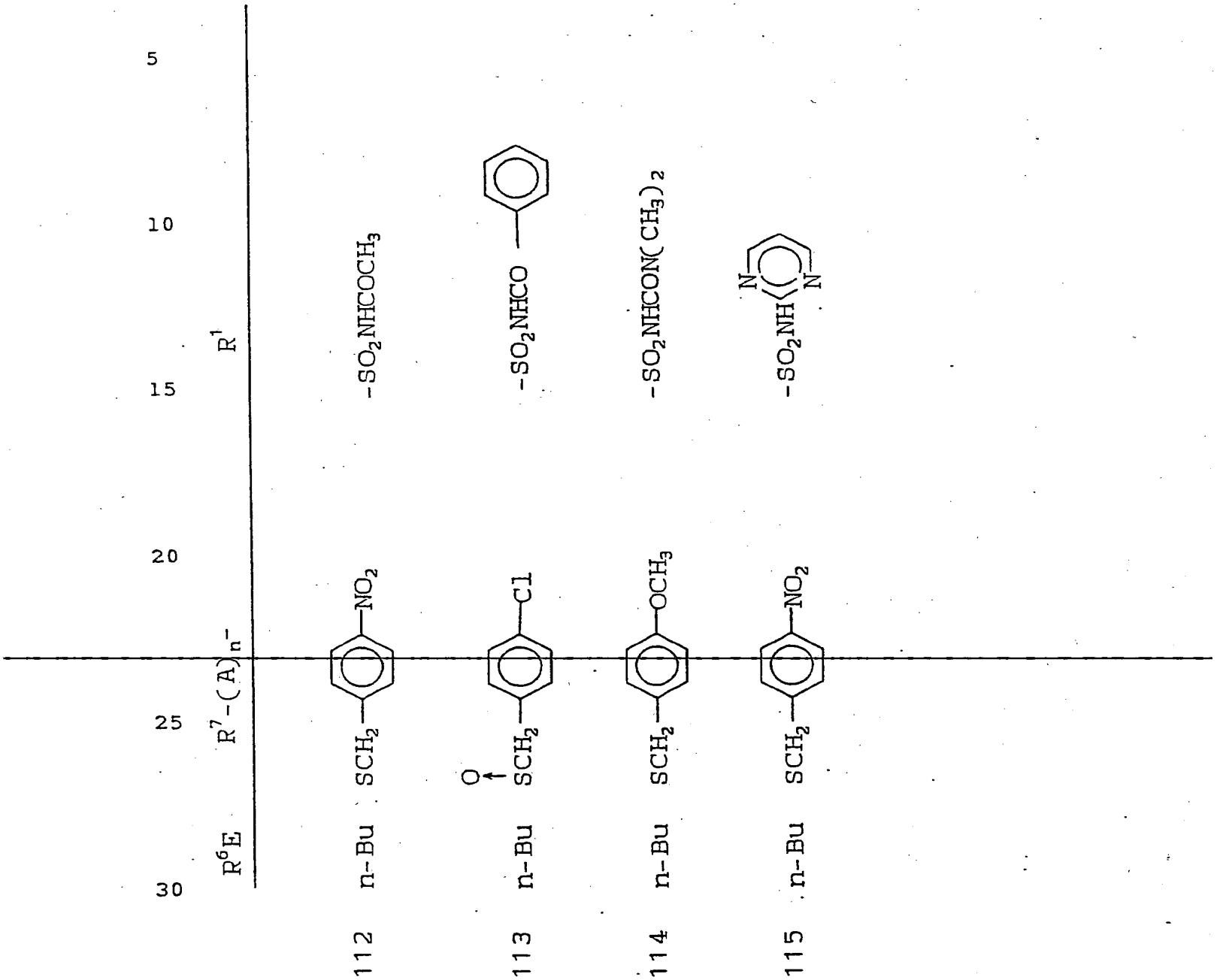
(I)

	R^6E	$R^7(A)_n$-	mp	formula	Analysis	C	H	N
93	n-Bu		130-132°C dec.	$C_{29}H_{30}N_8O_2S \cdot 0.5H_2O$	calcd:	61.79	5.54	19.88
					found:	61.50	5.52	19.78
94	n-Bu		135-137°C	$C_{29}H_{30}N_8O_3S \cdot 0.25H_2O$	calcd:	60.42	5.43	19.05
				$\cdot 0.15C_4H_8O_2$ (ethyl acetate)	found:	60.25	5.60	18.88
95	n-Bu							
96	n-Bu							

	R^6E	$R^7-(A)_n-$	mp	Formula	Analysis C	H	N
97	n-Bu						
98	n-Bu						
99	n-Bu						
100	n-Bu						

	R^6E	$R^7-(A)_n-$	mp	formula	Analysis C	H	N
101	n-Bu						
102	n-Bu						
103	n-Bu						
104	n-Bu						

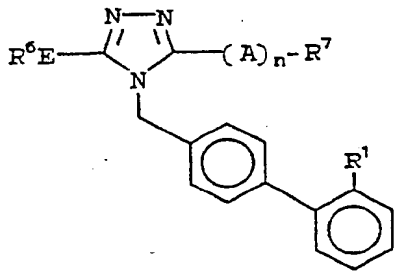
	R^6E	$R^7-(A)_n-$	mp	Formula	Analysis C	H	N
105	n-Bu						
106	n-Bu						
107	n-Bu						
108	n-Bu						



	R^6E	$R^7-(A)_n-$	R^1
112	n-Bu	SCH_2 — NO_2	$-SO_2NHCOCH_3$
113	n-Bu	SCH_2 — O — Cl	$-SO_2NHCO$ —
114	n-Bu	SCH_2 — OCH_3	$-SO_2NHCON(CH_3)_2$
115	n-Bu	SCH_2 — NO_2	$-SO_2NH$ — N=N

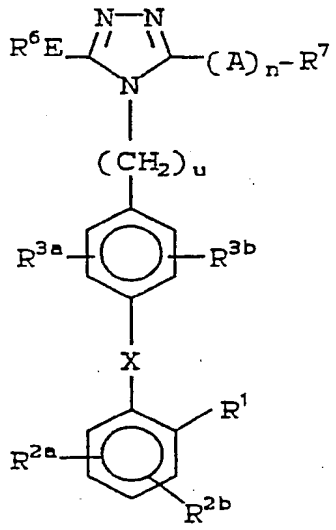
EXAMPLES 109-115

The following compounds of formula (I) can be prepared according to Schemes 20-22 (and earlier Schemes referred to therein).



WHAT IS CLAIMED IS:

1. A method of treating gastrointestinal disorders which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of structural formula:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is

(a) $-NHSO_2R^{23}$,
(b) $-NHSO_2NHCOR^{23}$,
(c) $-NHCONHSO_2R^{23}$,
(d) $-SO_2NHR^{23}$,
(e) $-SO_2-NHCOR^{23}$,
(f) $-SO_2NHCONR^9R^{23}$,

(g) $-SO_2NHCOOR^{23}$,
(h) $-SO_2NHOR^{23}$,
(i) $-CH_2SO_2NHCOR^{23}$,
(j) $-CH_2SO_2NHCONHR^{23}$,
(k) $-CO_2H$, or
(l) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are each independently:
(a) hydrogen,
(b) Cl, Br, I, F,
(c) CF_3,
(d) C_1-C_4-alkyl, or
(e) C_1-C_4-alkoxy;

R^{3a} is
(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,
(d) C_1-C_6-alkoxy, or
(e) C_1-C_6-alkoxy-C_1-C_4-alkyl;

R^{3b} is
(a) H,
(b) Cl, Br, I, F,
(c) C_1-C_6-alkyl,
(d) C_3-C_6-cycloalkyl,
(e) C_1-C_6-alkoxy, or
(f) CF_3;

R^4 is H, C_1-C_6 alkyl, benzyl or phenyl;

R^5 is H or $-\overset{R^4}{\underset{|}{C}}H-O-\overset{O}{\overset{||}{C}}-R^4$;

E is a single bond, $-NR^{13}(CH_2)_s-$, $-S(O)_x(CH_2)_s-$ where x is 0 to 2 and s is 0 to 5, $-CH(OH)-$, $-O(CH_2)_s-$, $-CO-$;

R^6 is

(a) aryl, wherein aryl is defined as phenyl or naphthyl which can be unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, C_3-C_7-cycloalkyl, C_2-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above, $-O-C_1-C_4$-alkyl, C_3-C_7-cycloalkyl, Cl, Br, I, F, $-OH$, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, $-S-C_1-C_4$-alkyl;

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring which can contain one or two members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of $-OH$, $-SH$, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, Cl, Br, I, F, or NO_2;

(d) mono-, di-, tri- or perfluoro-C_1-C_5-alkyl;

(e) C_3-C_7-cycloalkyl, unsubstituted or substituted with one or more substituents selected from the group consisting of

C_1-C_4-alkyl, -O-C_1-C_4-alkyl, -S-C_1-C_4-alkyl, -OH, perfluoro-C_1-C_4-alkyl or Cl, Br, F, I;

(f) C_3-C_7-cycloalkyl-C_1-C_3-alkyl wherein the cycloalkyl is substituted as in (e) above;

A is $S(O)_p$, -O- NHC(=O)-, $-C(=O)NR^{13}-$, or $-NR^{13}-$, wherein p is 0 to 2;

R^7 is

(a) C_1-C_{10}-alkyl;

(b) substituted C_1-C_{10} alkyl in which one or more substituent(s) is selected from

(1) Cl, Br, I, F,

(2) hydroxy,

(3) C_1-C_{10}-alkoxy,

(4) C_1-C_5-alkoxycarbonyl,

(5) C_1-C_4-alkylcarbonyloxy,

(6) C_3-C_8-cycloalkyl,

(7) phenyl,

(8) substituted phenyl in which the substituents are V and W,

(9) C_1-C_{10}-alkyl-$S(O)_p$,

(10) C_3-C_8-cycloalkyl-$S(O)_p$,

(11) phenyl-$S(O)_p$,

(12) substituted phenyl-$S(O)_p$ in which the substituents are V and W,

(13) oxo,

(14) carboxy,

(15) NR^9R^{10},

(16) C_1-C_5-alkylaminocarbonyl,

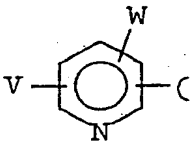
(17) di(C_1-C_5-alkyl)aminocarbonyl,

(18) cyano;

(c) perfluoro-C_1-C_4-alkyl,
(d) C_2-C_{10}-alkenyl,
(e) C_2-C_{10}-alkynyl,
(f) C_3-C_8-cycloalkyl,
(g) substituted C_3-C_8-cycloalkyl in which one or more substituent(s) is selected from:
(1) Cl, Br, I, F,
(2) hydroxy,
(3) C_1-C_{10}-alkoxy,
(4) C_1-C_5-alkoxycarbonyl,
(5) C_1-C_4-alkylcarbonyloxy,
(6) C_3-C_8-cycloalkyl,
(7) phenyl,
(8) substituted phenyl in which the substituents are V and W,
(9) C_1-C_{10}-alkyl-$S(O)_p$ in which p is 0 to 2,
(10) C_3-C_8-cycloalkyl-$S(O)_p$,
(11) phenyl-$S(O)_p$,
(12) substituted phenyl-$S(O)_p$ in which the substituents are V and W,
(13) oxo,
(14) carboxy,
~~(15) NR^9R^{10},~~
(16) C_1-C_5-alkylaminocarbonyl,
(17) di(C_1-C_5-alkyl)aminocarbonyl,
(18) cyano,
(19) C_1-C_4-alkylcarbonyl;
(20) (C_1-C_5) alkyl,
(h) phenyl,
(i) substituted phenyl in which the substituents are V and W,

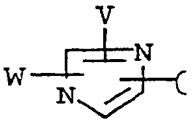
(j) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,

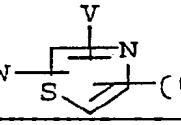
(k) substituted aryl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which the phenyl group is substuted with V and W;

(l) 

(m) 

(n) 

(o) 

(p) 

with the proviso that when E is a single bond and n is 0, then R^7 is:

(a) substituted C_1-C_{10}-alkyl in which one or more substituent(s) is selected from:

(1) C_3-C_8-cycloalkyl,

(2) phenyl,

(3) substituted phenyl in which the substituents are V and W,

(4) C_3-C_8-cycloalkyl-$S(O)_p$ where p is 0 to 2,

(5) phenyl-$S(O)_p$ where p is 0 to 2,

(6) substituted phenyl-$S(O)_p$ where p is 0 to 2 and the substituents are V and W:

(b) CF_3;

(c) C_3-C_8-cycloalkyl;

(d) substituted C_3-C_8-cycloalkyl in which the substituent is selected from:

(1) C_1-C_5-alkyl,

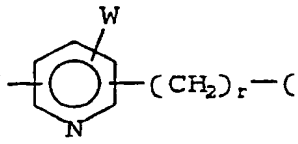
(2) C_1-C_5-alkoxy;

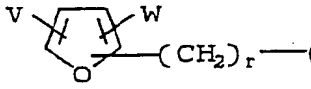
(e) phenyl,

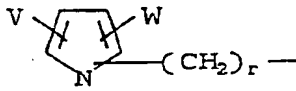
(f) substituted phenyl as defined above in which the substituents are V and W;

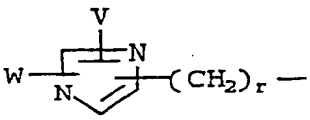
(g) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which b is 0 when B is -C(O)-;

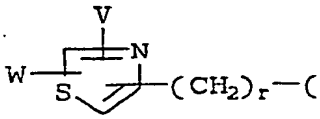
(h) substituted phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which b is 0 when B is -C(O)- and the phenyl group is substituted with V and W;

(i)  ,

(j)  ,

(k)  ,

(l)  ,

(m)  ,

n is 0 or 1;

B is -C(O)-, -S-, or -O-, $-NR^4$, $-NR^4C(O)-$, or $-C(O)NR^4$;

b is 0 or 1;

r and t are 0 to 2;

u is 1 or 2;

p is 0 to 2;

V and W are each independently selected from:

(a) H,
(b) C_1-C_5-alkoxy,
(c) C_1-C_5-alkyl,
(d) hydroxy,
(e) C_1-C_5-alkyl-$S(O)_p$,
(f) -CN,
(g) $-NO_2$,
(h) $-NR^9R^{10}$;
(i) C_1-C_4-alkyl-$CONR^9R^{10}$,
(j) $-CO_2R^9$,
(k) C_1-C_5-alkyl-carbonyl,
(l) trifluoromethyl,
(m) Cl, Br, I, F,
(n) hydroxy-C_1-C_4-alkyl,
(o) C_1-C_4-alkyl-CO_2R^9,
(p) -1H-tetrazol-5-yl,
(q) $-NHSO_2CF_3$,
(r) aryl,
(s) $-OCONR^9R^{10}$,
(t) $-NR^4CO_2R^9$,
(u) $-NR^4CONR^9R^{10}$,
~~(v) $-NR^4CON(CH_2CH_2)_2Q$ where Q is O, $S(O)_p$ or NR^9,~~
(w) $-OCON(CH_2CH_2)_2Q$, or
(x) $-CONR^9R^{10}$;

R^9 is H, C_1-C_5-alkyl, phenyl or benzyl;

R^{10} is H, C_1-C_4-alkyl; or,

R^9 and R^{10} together may be $-(CH_2)_m-$ where m is 3-6;

R^{11} is H, C_1-C_6-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, or $-CH_2-C_6H_4R^{20}$;

R^{12} is $-CN$, $-NO_2$ or $-CO_2R^4$;

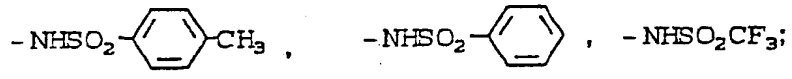
R^{13} is H, C_1-C_4-acyl, C_1-C_6-alkyl, allyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{14} is H, C_1-C_8-alkyl, C_1-C_8-perfluoroalkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{15} is H, C_1-C_6-alkyl, hydroxy;

R^{16} is H, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, phenyl or benzyl;

R^{17} is $-NR^9R^{10}$, $-OR^{10}$, $-NHCONH_2$, $-NHCSNH_2$,



R^{18} and R^{19} are independently C_1-C_4-alkyl or taken together are $-(CH_2)_q-$ where q is 2 or 3;

R^{20} is H, $-NO_2$, $-NH_2$, $-OH$ or $-OCH_3$;

R^{21} is C_1-C_5 alkyl or CF_3;

R^{22} is

(a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, or F, $-O-C_1-C_4$-alkyl, C_1-C_4-alkyl, $-NO_2$, $-CF_3$, $-SO_2NR^9R^{10}$, $-S-C_1-C_4$-alkyl, $-OH$, $-NH_2$, $-COOR^4$, C_3-C_7-cycloalkyl, and C_3-C_{10}-alkenyl;

(b) C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C_3-C_7-cycloalkyl, Cl, Br, I, F, $-OH$, $-O-C_1-C_4$-alkyl, $-NH_2$, $-NH(C_1-C_4$-alkyl), $-N(C_1-C_4$-alkyl$)_2$, $-NH-SO_2R^4$, $-COOR^4$, $-SO_2NHR^9$, and $-S-C_1-C_4$-alkyl;

(c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring comprising one or two heteroatoms selected from the group consisting of N, O, and S, and wherein the substituents are members selected from the group consisting of: $-OH$, $-SH$, C_1-C_4-alkyl, C_1-C_4-alkyloxy, $-CF_3$, $-COOR^4$, Cl, Br, I, F, and NO_2; or

(d) C_3-C_7-cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: C_1-C_4-alkyl, $-O-C_1-C_4$-alkyl, $-S-C_1-C_4$-alkyl, $-OH$, $-COOR^4$, C_1-C_4-perfluoroalkyl, Cl, Br, F, and I, or

(e) (C_1-C_4)-perfluoroalkyl;

R^{23} is

(a) aryl,

(b) heteroaryl,

(c) C_3-C_7-cycloalkyl,

(d) C_1-C_4-alkyl unsubstituted or substituted with a substituent selected from the group consisting of aryl, heteroaryl, -OH, -SH, C_1-C_4-alkyl, -O(C_1-C_4-alkyl), -S(C_1-C_4-alkyl), $-CF_3$, Cl, Br, F, I, $-NO_2$, $-CO_2H$, $-CO_2$-C_1-C_4-alkyl, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$, $-N(CH_2CH_2)_2L$ where L is a single bond, CH_2, O, $S(O)_p$ or NR^9, $-PO_3H$, -PO(OH)(O-C_1-C_4-alkyl);

X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $-\underset{\displaystyle R^{13}}{\overset{|}{N}}-$,

(f) $-CO\underset{\displaystyle R^{15}}{\overset{|}{N}}-$,

(g) $-NCO\underset{\displaystyle R^{15}}{\overset{|}{-}}$,

(h) $-OCH_2-$,

(i) $-CH_2O-$

(j) $-SCH_2-$,

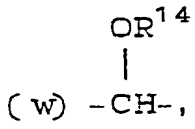
(k) $-CH_2S-$,

(l) $-NHC(R^9)(R^{10})-$,

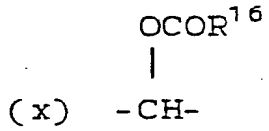
(m) $-NR^9SO_2-$,

(n) $-SO_2NR^9-$,

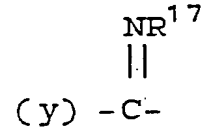
(o) $-C(R^9)(R^{10})NH-$,
(p) $-CH=CH-$,
(q) $-CF=CF-$,
(r) $-CH=CF-$,
(s) $-CF=CH-$,
(t) $-CH_2CH_2-$,
(u) $-CF_2CF_2-$,
(v) 1,1 and 1,2-disubstituted cyclopropyl,



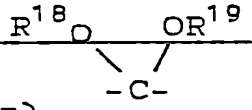
(w) $-CH-$,



(x) $-CH-$



(y) $-C-$, or



(z) ; and

Z is O, NR^{13} or S.

2. The method of Claim 1 wherein:

R^1 is:

(a) $-SO2NHCOR^{23}$,
(b) $-SO_2NHCONR^9R^{23}$,
(c) $-SO_2NHCOOR^{23}$,
(d) $-SO_2NHOR^{23}$,
(e) $-CH_2SO_2NHCOR^{23}$, or
(f) -1H-tetrazol-5-yl;

R^{2a} is H;

R^{2b} is H, F, Cl, CF_3 or C_1-C_4-alkyl;

R^{3a} is H;

R^{3b} is H, F, Cl, CF_3, C_1-C_4-alkyl, C_5-C_6-cycloalkyl, $-COOCH_3$, $-COOC_2H_5$, $-SO_2-CH_3$, NH_2, $-N(C_1-C_4$-alkyl$)_2$ or $-NH-SO_2CH_3$;

E is a single bond, -O- or -S-;

R^6 is

(a) C_1-C_6 alkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, OH, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$ or phenyl;
(b) C_2-C_6-alkenyl or C_2-C_6-alkynyl;
(c) aryl unsubstituted or substituted with a substituent selected from the group consisting of Cl, F, Br, I, $-CF_3$, $-NO_2$, -OH, $-NH_2$, $-S-CH_3$, $-S-C_2H_5$, $-SO_2NH_2$ $-O-CH_3$;

(d) a heteroaryl selected from the group consisting of: 2-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, imidazoyl, thiazolyl, thienyl, or furyl;

(e) perfluoro-C_1-C_4-alkyl selected from CF_3, CF_3CF_2, $CF_3CF_2CF_2$, $CF_3CF_2CF_2CF_2$;

(f) C_3-C_7-cycloalkyl unsubstituted or substituted with a substituent selected from the group consisting of Cl, CF_3, OH, $-O-CH_3$, $-OC_2H_5$, $-S-CH_3$, $-S-C_2H_5$, CH_3, CH_2CH_3, CF_2CF_3, $(CF_2)_2CF_3$ or phenyl;

R^7 is:

(a) C_1-C_{10}-alkyl,

(b) substituted C_1-C_{10} alkyl in which one or two substituents are selected from:

(1) hydroxy,

(2) C_1-C_5-alkoxy,

(3) C_1-C_5-alkoxycarbonyl,

(4) C_1-C_4-alkylcarbonyloxy,

(5) C_3-C_8-cycloalkyl,

(6) phenyl,

(7) substituted phenyl in which the substituents are V and W,

(8) C_1-C_5-alkyl-$S(O)_p$

(9) phenyl-$S(O)_p$

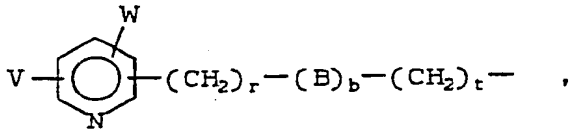
(10) substituted phenyl $S(O)_p$ in which the substituents are V and W,

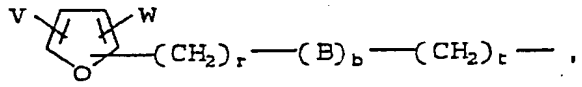
(11) oxo,

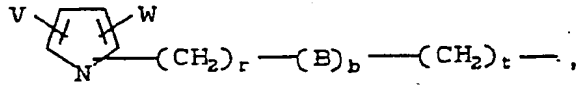
(12) carboxy,

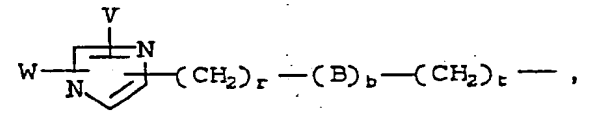
(13) C_1-C_5-alkylaminocarbonyl,
(14) di(C_1-C_5-alkyl)aminocarbonyl;

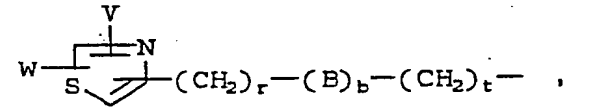
(c) CF_3,
(d) phenyl,
(e) substituted phenyl in which the substituents are V and W,
(f) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,
(g) substituted phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,

(h) 

(i) 

(j) 

(k) 

(l) 

A is -S-, -S(O)- or -O-;

V and W are independently selected from:

(a) hydrogen,
(b) C_1-C_5-alkoxy,
(c) C_1-C_5-alkyl,
(d) hydroxy,
(e) NR^9R^{10},
(f) CO_2R^9,
(g) trifluoromethyl,
(h) Cl, Br, I, F,
(i) hydroxy-C_1-C_4-alkyl-,
(j) -1H-tetrazol-5-yl,
(k) $-NHSO_2CF_3$,
(l) C_1-C_5-alkyl-$S(O)_p$-,
(m) -CN,
(n) $-NO_2$,
(o) C_1-C_4-alkyl-$CONR^9R^{10}$,
(p) C_1-C_5-alkylcarbonyl, or
(q) $-CONR^9R^{10}$;

u is 1; and

X is:

(a) carbon-carbon single bond,
(b) -C(O)-,
(c) $-NR^{15}C(O)-$.

3. The method of Claim 2 wherein:

E is a single bond or -S-;

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H; and

R^6 is C_1-C_6-alkyl.

4. The method of Claim 3 wherein:

R^7 is:

(a) C_1-C_{10}-alkyl,

(b) substituted C_1-C_{10}-alkyl in which one or two substituents are selected from:

(1) hydroxy,

(2) C_1-C_5-alkoxy,

(3) C_1-C_5-alkoxycarbonyl,

(4) phenyl,

(5) carboxy,

(6) C_1-C_5-alkylaminocarbonyl;

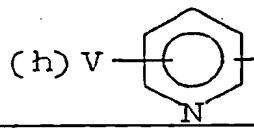
(c) CF_3,

(d) phenyl,

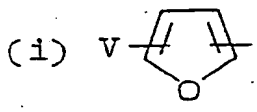
(e) phenyl substituted with V and W,

(f) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-,

(g) phenyl-$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- in which the phenyl is substituted with V and W,



(h) V- -$(CH_2)_r$-$(B)_b$-$(CH_2)_t$- or



(i) V- -$(CH_2)_r$-$(B)_b$-$(CH_2)_t$-;

V and W are selected from:

(a) hydrogen,

(b) C_1-C_5-alkyl,

(c) C_1-C_5-alkoxy,

(d) CO_2R^9,

(e) halogen,
(f) hydroxy-C_1-C_4-alkyl-,
(g) -1H-tetrazol-5-yl-,
(h) $-NHSO_2CF_3$,
(i) -CN,
(j) $-NO_2$; and

X is $-NR^{15}C(O)-$, or a carbon-carbon single bond.

5. The method of Claim 1 wherein the gastrointestinal disorder is selected from the group consisting of gastroesophagal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis.

6. A pharmaceutical composition useful in the treatment of gastrointestinal disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as recited in Claim 1.

7. The method of Claim 1 wherein the central nervous system disorder is selected from the group consisting of: psychoses, depression, cognitive dysfunction, anxiety, tardive dyskinesia, drug dependency, panic attack and mania.

8. A pharmaceutical composition useful in the treatment of central nervous system disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as recited in Claim 1.

9. The use of a compound of the formula I as defined in any of claims 1 to 4 for the treatment of a disorder as defined in any of claims 1, 5 or 7.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search R port)

Application number

GB 9300937.1

Relevant Technical fields

(i) UK Cl (Edition L) A5B (BHA BJA)

(ii) Int Cl (Edition 5) A61K 31/41

Search Examiner

J F JENKINS

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS-ONLINE

Date of Search

26 APRIL 1993

Documents considered relevant following a search in respect of claims 1 TO 9

Category (see over)	Identity of document and relevant passages		Relevant to claim(s)
X	EP 0409332 A2	(MERCK) see Claims 5 and 7	6 and 8
X	US 5015651	(DU PONT) see column 4 line 60 to column 7 line 20 Examples 67-169, column 80 line 24 to column 82 line 8 & EP 0323841 A2	6 and 8
PA	US 5155126	(DU PONT) see Claim 1	1

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

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